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REMARKS

I Status Of The Claims

Claims 1, 12, 14, 15, 18, and 19 have been amended. Claim 1 has been amended to clarify that the therapeutic agent is attached to the linker via an alcohol functional group present on the therapeutic agent. Claim 12 has been amended to limit the therapeutic agent to an anesthetic or sedative. Claim 14 has been amended, as suggested by the Examiner, to be directed to a composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier. Claim 15 has been amended to correct typographical errors, and to conform to U.S. practice. Claims 1, 18, and 19 have been amended to limit the therapeutic or pharmaceutical agent to a water-insoluble steroid, anesthetic or sedative.

Claim 21 has been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of claim 21 in future continuation application(s).

New claims 22-24 have been added. Support for claims 22-24 may be found in the specification at page 11, lines 26-28, pages 12 and 13, and in original claims 12, 13, and 21. No new matter has been added.

Claims 1-20 and 22-24 are pending in this application, and are currently at issue.

II Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-11, 15, and 16 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that the specification, while being enabling for compounds wherein phosphocholine is directly linked to steroids, is not enabling for attachment through the multitudes of linkers and moieties defined for X. The Examiner recites the *In re Wands* factors and concludes that the present invention could not be practiced without undue experimentation.

This rejection is not believed to be well taken, and is respectfully traversed.

The Examiner asserts that it is unclear if the multitude of compounds encompassed by claims 1-9 could in fact be prepared, and that even if they could, it is unclear whether they would retain the drug efficacy since it depends on the efficient release of the drug from the various linker units.

The Examiner's attention is directed to pages 14 and 15 of the specification, wherein synthetic routes for preparing the claimed drug-X-linker-therapeutic agent compounds are described. A claimed compound can be enabled without disclosing working examples of the preparation of the compound. "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. ¶2164.02.

The Examiner further contends that the specification gives no guidance at all in terms of how the various linkers and X moieties are attached to the various drugs. The Examiner states that the specification does not even recite these linkers and X moieties and the drugs claimed and concludes that in the absence of a broad basis of support in the specification with regard to what linker and X moiety may be attached to what drug, the claims must be limited to drugs directly attached to the phosphocholine.

Contrary to the Examiner's assertion, the specification does provide guidance as to how the linkers and X moieties are attached to the therapeutic agent. The Examiner's attention is directed to page 4, lines 1-10 of the specification, wherein the nature of the attachment is clearly set forth. Moreover, the nature of the linkers useful in the present invention is clearly defined at pages 5, line 1 to page 10, line 1 of the specification. Examples of therapeutic agents are clearly set forth in the section entitled "Examples of therapeutic agents which benefit from a phosphocholine agent" at pages 10 and 11 of the specification.

In view of the above, applicants submit that the specification is sufficiently enabling for claims 1-11, 15, and 16, and respectfully request that the rejection be withdrawn.

III Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 12, 14, 15, 18, and 21 have been rejected under 35 U.S.C. § 112, second paragraph for indefiniteness.

With respect to claim 12, the Examiner asserts that the phrase "related anesthetic or sedative compounds" is unclear, and that it is unclear what the term "Propofol" represents. Applicants submit that the amendments to claims 12 have overcome this rejection, and respectfully request that it be withdrawn.

For clarification, applicants wish to point out that "propofol" is the tradename for the anesthetic 2,6-diisopropylphenol. See page 2, lines 1-2 and page 16, lines 8-10 of the specification. For the Examiner's convenience, applicants enclose herewith, appended hereto as Exhibit 1, a copy of the Merck Index entry for propofol.

Claim 14 has been amended, as suggested by the Examiner, to be directed to a composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier. Accordingly, the rejection has been overcome, and should be withdrawn.

Claim 15 has been amended to delete the question mark recited therein. The rejection of this claim has been overcome.

The Examiner has requested clarification of claim 18. The Examiner asserts that claim 18 recites "increasing the aqueous solubility of a pharmaceutically active agent." The Examiner contends that an active agent conjugated to a lipophilic phospholipid would be more lipophilic, and hence less soluble, that the active agent itself.

Applicants respectfully submit that the Examiner is mistaken in characterizing phosphocholine as lipophilic. Phosphocholine (or phosphorylcholine) is a derivative of the hydrophilic molecule choline [$N(CH_3)_3$] which should not be confused with the lipophilic compound phosphatidylcholine, which is a derivative of glycerol. The latter contains two lipophilic fatty acid side chains. Appended hereto as Exhibit 2 is a page from the well known biochemistry textbook authored by Lubert Stryer showing the structure of phosphocholine and phosphatidlycholine.

Contrary to the Examiner's assertion, claim 18 does not recite "increasing the aqueous solubility of a pharmaceutically active agent." Moreover, the conjugation of the phosphocholine moiety to the therapeutic agent via the linker moiety X results in enhanced aqueous solubility, and increased bioavailability, of the therapeutic agent. As described at page 4, lines 1-21 of the specification, this formulation facilitates enzymatic cleavage of the phosphocholine linker bond and liberates the linker upon administration. The linker spontaneously eliminates, thereby liberating the therapeutic agent and an inert linker decomposition molecule. Increases of not less that 5-10 fold in the aqueous solubility, and bioavailability, are observed.

In view of the above, applicants respectfully request that the rejection of claim 18 be withdrawn.

Claim 21 has been canceled, rendering the rejection of this claim moot.

IV Claim Rejections Under 35 U.S.C. § 102

(i) Claims 1-11, 13-15, 18-19, and 21 have been rejected under 35 U.S.C. § 102(a) or (b) as anticipated by Chasalow (U.S. Patent No. 5,830,432, "Chasalow"). The Examiner contends that Chasalow discloses compounds wherein a drug is attached to phosphocholine through an NH_2 group ("X"), which in turn is attached to a substituted alkyl or alkenyl moiety ("linker") and methods of increasing the aqueous solubility of bioactive agents by conjugating them to

phosphocholine moieties. The Examiner asserts that Chasalow discloses steroids and aspirin as possible therapeutic agents.

Claim 21 has been canceled, rendering the rejection of this claim moot.

The rejection of claims 1-11, 13-15, 18 and 19 is respectfully traversed, on the grounds that Chasalow does not describe or suggest the claimed compounds, wherein the therapeutic agent is linked to the X moiety by an alcohol functional group. See page 4, lines 4-5 of the present specification. In contrast, the conjugates disclosed in Chasalow are all linked by a carboxyl group, not an alcohol group. In the Abstract, Chasalow states that the methods disclosed therein are for "increasing the aqueous solubility and bio-availability of bioactive agents having a free-carboxyl group...", and that "the target drugs have a carboxy group as the site of linkage to the phospholipid." See col. 3, lines 59-61. Moreover, at col. 2, lines 38-42, Chasalow asserts (emphasis added):

> The present invention is directed to increasing the bioavailability and/or aqueous solubility of pharmaceutically active agents, **specifically by conjugation of such agents via a free carboxy group** to a phospholipid . . .

Indeed, in all the specific conjugates disclosed in Chasalow, see for example, the last structures given at cols. 6 and 7, the drug is linked to the phosphocholine via a carboxy (C=O) linkage present on the therapeutic agent.

Chasalow is completely silent respecting a conjugate wherein the therapeutic agent is attached to the linker moiety via an alcohol functionality. Accordingly, Chasalow does not anticipate the present claims. Applicants respectfully request that the rejection be withdrawn.

(ii) Claims 1-11, 13-15, 18-19, and 21 have been rejected under 35 U.S.C. § 102(a) or (b) as anticipated by Ansell (U.S. Patent No. 5,534,499, "Ansell"). The Examiner contends that Ansell discloses taxol attached to phosphocholine through the claimed linker and X moieties.

Claim 21 has been canceled, rendering the rejection of this claim moot.

The rejection of claims 1-11, 13-15, 18 and 19 is respectfully traversed, on the grounds that the present claims are directed to therapeutic agents linked to a phosphocholine via a linker, wherein the therapeutic agent is a water insoluble steroid, anesthetic or sedative. The conjugate compounds disclosed in Ansell, as set forth at col. 4, lines 42-54, are antineoplastics, such as taxol and doxyrubicin, nucleoside drugs and retinoids. These are not steroids, anesthetics, or sedatives. Accordingly, Ansell does not anticipate the present claims. Applicants respectfully request that the rejection be withdrawn.

IV Claim Rejections Under 35 U.S.C. § 103

(i) Claims 12, 13, 16-17, and 20 have been rejected under 35 U.S.C. § 103(a) as obvious over Chasalow. The Examiner concedes that Chasalow does not teach attachment of the instant drugs, but concludes that in view of the suggestion that the method is applicable to any active agent, it would have been obvious to one of ordinary skill in the art to use any active agent with a reasonable chance of success.

This rejection is respectfully traversed.

As set forth above, Chasalow does not teach or suggest phosphocholine linked conjugates whereby the therapeutic agent is attached to a linking moiety via an alcohol. Indeed, Chasalow teaches away from the presently claimed compounds whereby the therapeutic agent is attached to a linking moiety via an alcohol, stating that the [Chasalow] invention is directed to increasing the bioavailability and/or aqueous solubility of pharmaceutically active agents, **specifically by conjugation of such agents via a free carboxy group** to a phospholipid. Therefore, one of ordinary skill in the art would have had no reasonable expectation of success that conjugates could be formed by linking the therapeutic agent to the phosphocholine by attached of the agent to a linker via an alcohol functionality.

Accordingly, the present claims are not obvious over Chasalow. Applicants respectfully request that the rejection be withdrawn.

(ii) Claims 12, 13, 16-17, and 20 have been rejected under 35 U.S.C. § 103(a) as obvious over Ansell. The Examiner acknowledges that Ansell does not teach the instant drugs, but concludes that in view of the suggestion that the method is applicable to any active agent, it would have been obvious to one of ordinary skill in the art to use any active agent with a reasonable chance of success.

This rejection is respectfully traversed.

Ansell teaches therapeutic agents capable of being formulated in liposomes or micelles, whereby the therapeutic agent is attached to a fatty acid chain of a phospholipid. As can be seen from col. 6, lines 3-5 of Ansell, the RC(O) group present in the compound of formula (III), and hence also in the compounds of Formula (IV) - (XI) of Ansell, is a fatty acid radical, such as lauroyl, myristoyl, plamitoyl, stearoyl, or oleoyl. In contrast, the compounds of the present invention do not rely upon emulsifiers or liposome or micelle formation in order to increase the solubility and bioavailability of the therapeutic agent. Rather, in the present invention, the therapeutic agent is conjugated to phosphocholine via a linker, inserted between the phosphocholine and an alcohol group on the therapeutic agent. This formulation facilitates enzymatic cleavage of the phosphocholine linker bond and liberates the linker, which then spontaneously eliminates to liberate the therapeutic agent and an inert molecule arising form the decomposed linker.

Based upon the teachings of Ansell, one or ordinary skill in the art would have had no expectation of success that non liposomal or micellular formulated phosphocholine conjugated therapeutic agents could be prepared wherein the therapeutic agent was not conjugated to a fatty acid radical of the phosphocholine.

Ansell simply does not teach or suggest the presently claimed conjugates containing the linkers of the present invention attached between the therapeutic agent and the phosphocholine.

Accordingly, the present claims are not obvious over Ansell. Applicants respectfully request that the rejection be withdrawn.

In view of the above amendments and arguments, the pending claims in this application are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: June 25, 2004

Respectfully submitted,

By Howard M. Frankfort

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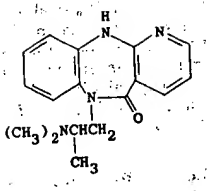
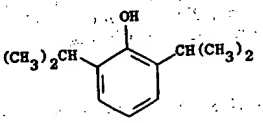


mp 122°.

Hydrochloride, $C_{17}H_{21}ClN_4O$, *UP 106, Depressin, Vagran.* mp 235°.

THERAP CAT: Antidepressant.

7847. Propofol. *2,6-Bis(1-methylethyl)phenol; 2,6-diisopropylphenol;* disoprofol; ICI 35868; Diprivan; Disoprivan; Rapinovet. $C_{12}H_{18}O$; mol wt 178.27. C 80.85%, H 10.18%, O 8.97%. Prepn: A. J. Kolka *et al., J. Org. Chem.* **21,** 712 (1956); **22,** 642 (1957); G. G. Ecke, A. J. Kolka, U.S. pat. 2,831,898 (1958 to Ethyl Corp.); T. J. Kealy, D. D. Coffman, *J. Org. Chem.* **26,** 987 (1961); B. E. Firth, T. J. Rosen, U.S. pat. 4,447,657 (1984 to Universal Oil Products). Chromatographic study: J. K. Carlton, W. C. Bradbury, *J. Am. Chem. Soc.* **78,** 1069 (1956). Animal studies: J. B. Glen, *Brit. J. Anaesth.* **52,** 731 (1980). Pharmacokinetics: H. K. Adam *et al., ibid.* 743; *idem, ibid.* **55,** 97 (1983). Determin in blood: *eidem, J. Chromatog.* **223,** 232 (1981). Comparative studies vs other injectable anesthetics: B. Kay, D. K. Stephenson, *Anaesthesia* **35,** 1182 (1980); D. V. Rutter *et al., ibid.* 1188. Use in i.v. anesthesia: E. Major *et al., ibid.* **37,** 541 (1982). Cardiovascular effects: D. Al-Khudhairi *et al., ibid.* 1007. Pharmacology of emulsion formulation: J. B. Glen, S. C. Hunter, *Brit. J. Anaesth.* **56,** 617 (1984). Series of articles on pharmacology and clinical experience: *Postgrad. Med. J.* **61,** Suppl. 3, 1-169 (1985).



bp_{30} 136°. bp_{17} 126°. mp 19°. n_D^{20} 1.5134. n_D^{25} 1.5111. d_{20} 0.955.

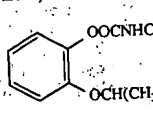
THERAP CAT: Anesthetic (intravenous).

THERAP CAT (VET): Intravenous anesthetic (dogs and cats).

7848. Propolis. Bee bread; hive dross. A resinous substance found in beehives. Collected by bees from buds. Soln of caffeic acid from propolis: Cizmárik, Matel, *Experientia* **26,** 713 (1970). Antimicrobial constituents of propolis: J. Metzner *et al., Pharmazie* **30,** 799 (1975); E. M. Schneidewind *et al., ibid.* 803. Review on the origin, chemical constituents and therapeutic activity: M. H. Haydak, *State of Iowa, Repts. State Apiarist 1953,* p 74-87; M. Vanhaelen, R. Vanhaelen-Fastre, *J. Pharm. Belge* **34,** 253 (1979).

Greenish-brown, sticky mass. Aromatic odor. d 1.2. mp 64°. Becomes brittle when cooled below 15°. Extraction with alcohol gives *propolis wax.* The residue from the alcohol extraction is called *propolis resin,* yielding *propolis balsam* on extraction with hot petr ether. Propolis balsam has a hyacinth odor and is said to contain 10% cinnamyl alcohol.

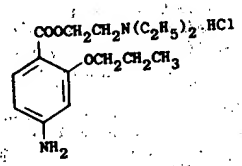
7849. Propoxur. *2-(1-Methylethoxy)phenol methylcarbamate; o-isopropoxyphenyl N-methylcarbamate;* aprocarb; BAY 39007; BAY 9010; Baygon; Bifex; Blattanex; Invisi-Gard; Propyon; Suncide; Sendran; Unden. $C_{11}H_{15}NO_3$; mol wt 209.24. C 63.14%, H 7.23%, N 6.69%, O 22.94%. Prepn: U.S. pat. 3,111,539 (1963 to Bayer; Chemagro Corp.). Properties: *Pflanzenschutz Nachr. Bayer* **18,** 53 (1965). Toxicity data: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969). Teratogenicity study: K. D. Courtney *et al., J. Environ. Sci. Health* **B20,** 373 (1985).



Minute crystals, mp 91.5°. Dec at high temp forming methyl isocyanate. Sol in methanol, acetone and many organic solvents, but only slightly sol in cold hydrocarbons. Water soly about 0.2% at 20°. Unstable in highly alkaline media. LD_{50} orally in male, female rats: 83, 86 mg/kg (Gaines).

USE: Insecticide.

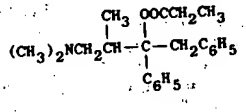
7850. Propoxycaine Hydrochloride. *4-Amino-2-propoxybenzoic acid 2-diethylaminoethyl ester hydrochloride; 2-diethylaminoethyl 4-amino-2-propoxybenzoate hydrochloride;* 2-diethylaminoethyl 2-propoxy-4-aminobenzoate hydrochloride; Ravocaine hydrochloride; Pravocaine hydrochloride; Blockaine hydrochloride. $C_{16}H_{27}ClN_2O_3$; mol wt 330.86. C 58.08%, H 8.23%, Cl 10.72%, N 8.47%, O 14.51%. Prepn: Clinton, Laskowski, U.S. pat. 2,689,248 (1954 to Sterling Drug).



White, odorless crystals, mp 148-150°. Discolors upon prolonged exposure to light and to air. Freely sol in water; sol in ethanol, chloroform. Sparingly sol in ether. Practically insol in acetone, chloroform. pH of a 2% aq soln 5.4.

THERAP CAT: Local anesthetic.

7851. Propoxyphene. *[S-(R*,S*)]-α-[2-(Dimethylamino)-1-methylethyl]-α-phenylbenzeneethanol propanoate (ester); α-d-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol propionate;* (+)-1,2-diphenyl-2-propionoxy-3-methyl-4-dimethylaminobutane; (+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane; *d*-propoxyphene; dextropropoxyphene. $C_{22}H_{29}NO_2$; mol wt 339.48. C 77.83%, H 8.61%, N 4.13%, O 9.43%. Prepn of racemate: Pohland, Sullivan, *J. Am. Chem. Soc.* **75,** 4458 (1953); Pohland, U.S. pat. 2,728,779 (1955 to Lilly). Prepn of (+)-form: Pohland, Sullivan, *J. Am. Chem. Soc.* **77,** 3400 (1955). Stereochemistry: Sullivan *et al., J. Org. Chem.* **28,** 2381 (1963); Casy, Myers, *J. Pharm. Pharmacol.* **16,** 455 (1964). Stereospecific synthesis: Pohland *et al., J. Org. Chem.* **28,** 2483 (1963). Metabolism: S. L. Due *et al., Biomed. Mass Spectrom.* **3,** 217 (1976). The α-*dl*- and *d*-diastereoisomers possess marked analgesic activity in contrast to the β-diastereoisomers which are substantially inactive. Toxicity: E. I. Goldenthal, *Toxicol. Appl. Pharmacol.* **18,** 185 (1971); J. L. Emerson *et al., ibid.* **19,** 445 (1971). Comprehensive description: B. McEwan in *Analytical Profiles of Drug Substances* **vol. 1,** K. Florey, Ed. (Academic Press, New York, 1972) pp 301-318. Symposium on pharmacology, toxicology, and clinical efficacy of propoxyphene alone and in combination with acetaminophen: *Human Toxicol.* **3,** Suppl., 1S-238S (1984).



Crystals from petr ether, mp 75-76°. $[\alpha]_D^{25}$ +67.3° (c = 0.6 in chloroform).

α-*d*-Hydrochloride, $C_{22}H_{30}ClNO_2$, *Algafan, Antalvic, Darvon, Depromic, Deprancol, Develin, Dolene, Dolocap, Doraphen, Erantin, Femadol, Harmar, Propox, Propoxychel, Proxagesic.* Bitter crystals from methanol + ethyl acetate, mp 163-168.5°. $[\alpha]_D^{25}$ +59.8° (c = 0.6 in water). Sol in water, alc, chloroform, acetone. Practically insol in benzene, ether. LD_{50} in mice, rats (mg/kg): 28, 15 i.v.; 111, 58 i.p.; 211, 134 s.c.; 282, 230 orally (Emerson).

α-*d*-Form napsylate monohydrate; $C_{32}H_{37}NO_5S.H_2O$, *Darvon-N, Doloxene.* LD_{50} orally in female rats: 990 mg/kg (Goldenthal).

α-*l*-Form, *see* Levopropoxyphene.

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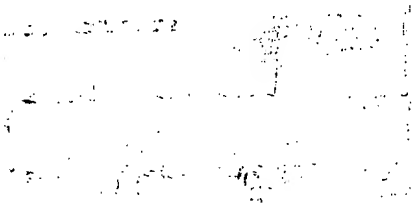

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PHOSPHOGLYCERIDES CAN ALSO BE SYNTHESIZED FROM A CDP-ALCOHOL INTERMEDIATE

In mammals, phosphatidyl choline is synthesized by a pathway that utilizes choline obtained from the diet (Figure 23-2). Choline is phosphorylated by ATP to *phosphorylcholine,* which then reacts with CTP to form *CDP-choline.* The phosphorylcholine unit of CDP-choline is then transferred to a diacylglycerol to form *phosphatidyl choline.* Note that the activated species in this pathway is the cytidine derivative of phosphorylcholine rather than of phosphatidate.

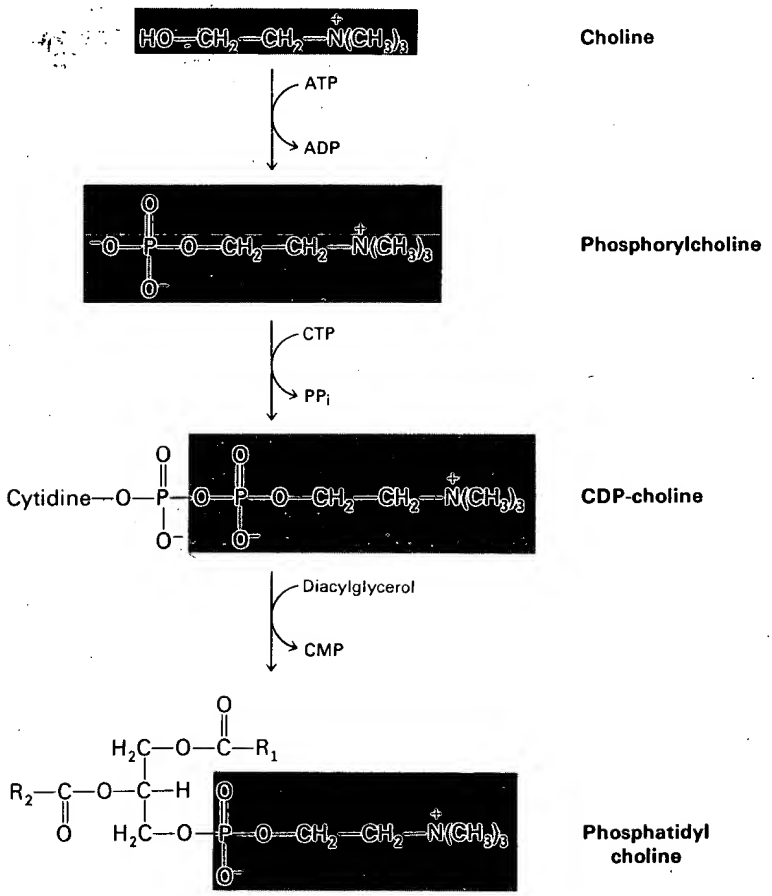


Figure 23-2
Synthesis of phosphatidyl choline.

Likewise, *phosphatidyl ethanolamine* can be synthesized from ethanolamine by forming a CDP-ethanolamine intermediate by analogous reactions. Alternatively, phosphatidyl ethanolamine can be formed from phosphatidyl serine by the enzyme-catalyzed exchange of ethanolamine for the serine moiety of the phospholipid.

PLASMALOGENS AND OTHER ETHER PHOSPHOLIPIDS ARE FORMED FROM DIHYDROXYACETONE PHOSPHATE

Some phospholipids contain an ether unit instead of an acyl unit at C_1. *Glyceryl ether phospholipids* are synthesized starting with dihydroxyacetone phosphate (Figure 23-3). Acylation by a fatty acyl CoA yields a 1-acyl derivative that exchanges with a long-chain alcohol to form an ether at C_1. The keto group at C_2 is reduced by NADPH, and the

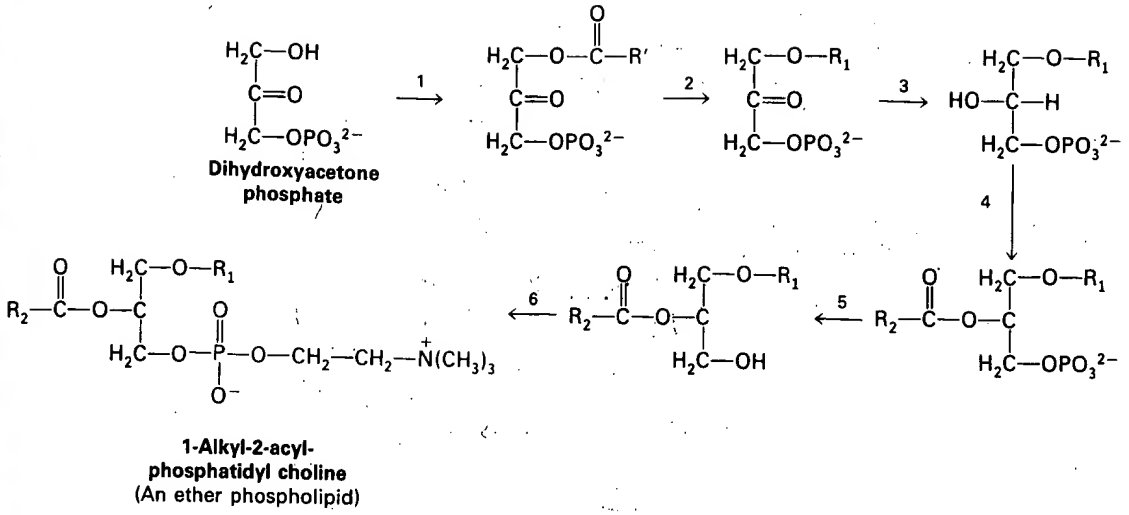
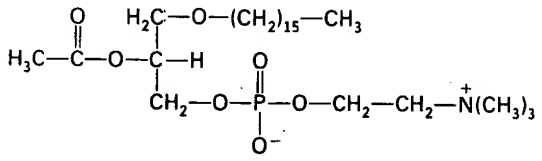


Figure 23-3
Synthesis of an ether phospholipid. The steps are (1) acylation by fatty acyl CoA, (2) exchange of an alcohol for the carboxylate moiety, (3) reduction by NADPH, (4) acylation by a second fatty acyl CoA, (5) hydrolysis of the phosphate ester, (6) transfer of a phosphocholine moiety.

resulting alcohol is acylated by a long-chain CoA. Removal of the 3-phosphate group yields 1-alkyl-2-acylglycerol, which reacts with CDP-choline to form the ether analog of phosphatidyl choline.

An ether phospholipid with striking activities has recently been identified. *Platelet-activating factor* is a 1-alkyl-2-acetyl ether analog of phosphatidyl choline. Even a very low concentration of this compound (0.1 nM) in the blood causes the aggregation of platelets and the dilation of blood vessels. The presence of an acetyl group rather than a long-chain acyl group at C_2 increases the water-solubility of this lipid, enabling it to function in an aqueous environment.



Plasmalogens are phospholipids containing an α,β-unsaturated ether at C_1. Phosphatidal choline, the plasmalogen corresponding to phosphatidyl choline, is formed by desaturation of a 1-alkyl precursor. The desaturase catalyzing this final step in the synthesis of a plasmalogen is a microsomal enzyme akin to the one that introduces double bonds into long-chain fatty acyl CoAs: O_2 and NADH are reactants, and cytochrome b_5 participates in catalysis (p. 489).